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CLINICAL REVIEW

Abbott, Biologic Licensing Application

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Adalimumab - for use in the treatment of rheumatoid arthritis

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I. Introduction

A. Background

Rheumatoid arthritis (RA) is a chronic, inflammatory disorder of the joints with a female predominance. A prevalence of 1% has been reported in the adult population. The disease is characterized by a progressive inflammatory synovitis manifested by polyarticular joint swelling and tenderness. The synovitis results in erosion of articular cartilage and marginal bone with subsequent joint destruction. RA produces substantial morbidity and increased mortality. Studies of natural history of the disease indicate that within 2 years of diagnosis, patients usually experience moderate disability; after 10 years 30% are severely disabled. Assessment of the efficacy of any treatment for RA entails clinical, physical function, and laboratory measures i.e., a composite measure of disease activity improvement.

The FDA issued a Guidance Document for evaluating new treatments of RA in February 1999 (Clinical Development Programs for Drugs, Devices, and Biological Products Intended for the Treatment of Rheumatoid Arthritis). The guidance document recognized claims for efficacy based on improvement in signs and symptoms and a group of enhanced claims. For demonstration of efficacy, the standards set forth requires improvement in signs and symptoms of RA in a clinical trial of at least six months duration based on validated composite endpoints or indices of signs and symptoms such as the American College of Rheumatology (ACR) criteria for 20% improvement (the ACR20). Demonstration of effectiveness in inhibition of progression of structural damage, assessed via a method like the modified Sharp score, requires a clinical trial of at least twelve months duration. Since RA is a chronic disease, demonstration of durability of efficacy is also expected. For products with the potential to elicit antibody formation, assessment for durability is particularly important, since antibodies that develop over time may block effectiveness.

The enhanced claims recognized in the RA Guidance Document include the ability to achieve: a major clinical response, defined as an ACR70 for six consecutive months; a complete clinical response, defined using ACR criteria for remission and no radiographic progression for six consecutive months while receiving ongoing drug therapy; and a remission, defined as a remission by ACR criteria and no radiographic progression for six consecutive months while off all anti-rheumatic therapy. To encourage long-term trials, the claim of improvement in physical function requires a validated measure of improvement in disability such as the HAQ (Health Assessment Questionnaire), Arthritis Impact Measure Scale (AIMS), as well as evidence of improvement or, at least, no worsening in a measure of health related-quality of life such as the SF-36 for two to five years. The E1A ICH guidance document recommends that for chronically administered products, the minimum safety data-base requires at least 300-600 patients treated with the recommended dose for at least six months, at least 100 patients treated for at least twelve months, and a total of 1000 to 1500 patients treated overall. However, longer term data may be required if late developing AEs are observed or if AEs are observed that increase in severity or frequency over time. In addition, more data may be required if there are

concerns based on preclinical toxicity testing, pharmacology, or inferences from similar agents.

Current drug therapy for RA includes non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids to provide symptomatic relief. Some disease-modifying antirheumatic drugs (DMARDs) have been demonstrated to inhinit disease progression; some patients fail to achieve an adequate or sustained response to therapy due to lack of efficacy or toxicity.

The recent introduction of new classes of therapeutic agents has contributed to major advances in the treatment of RA. The first TNF-α blocking agents, infliximab and etanercept, were approved for improvement in signs and symptoms of RA. In addition, the TNF-α blockers have demonstrated inhibition of progression of structural joint damage among patients with RA. More recently anakinra, the first IL-1 blocking agent, has been approved for improvement in signs and symptoms of RA. All three of these agents are generally well tolerated, but have been associated with uncommon serious adverse events, primarily serious infections.

These newer novel biological agents inhibit the action of cytokines, hormone-like proteins that mediate communication between cells, and play critical roles in normal biologic processes, such as cell growth, inflammation, and immunity. Both tumor necrosis factor (TNF-α) and interleukin-1 (IL-1) have been implicated in the progression of inflammatory synovitis and articular matrix degradation. Being foreign proteins, these biologic agents are potentially immunogenic, and studies have been carried out to determine whether antibodies over time diminish clinical activity and increase the incidence of adverse events. Treatment with infliximab has been associated with antibody formation, particularly in patients receiving treatment without concurrent MTX. Antibody-positive patients were more likely to experience infusion reactions.

B. Adalimumab Clinical Development Program

Adalimumab is a human-derived recombinant IgG1 monoclonal antibody engineered by gene technology. Adalimumab binds to TNF-α but not TNF-β and has a half-life of approximately 2 weeks. This antibody has been extensively studied *in vitro* as well as *in vivo* and no major toxicity was observed in animal studies. This submission presents data from three phase III clinical trials and assesses the efficacy and safety of adalimumab in the treatment of RA. Since TNF-α is an important cytokine affecting inflammation and immunity, patients were closely monitored and data were submitted for possible adverse events (AE), especially serious infections, malignancies, and immunogenic potential. In addition, the possible role of human antibodies to adalimumab on efficacy and safety was evaluated.

The adalimumab clinical development program includes 23 studies, 17 of which were conducted in RA patients, four of these studies (DE009, DE011, DE019, and DE031) represent controlled trials assessing the effectiveness of adalimumab, and four clinical pharmacology studies (DE015, DE024C, DE024J, and DE029) performed in healthy

volunteers. Figure 1 depicts the overall group of studies in the adalimumab clinical development program. Table 1 lists the studies that are discussed and provides summary information on studies providing evidence of efficacy. Patients treated concomitantly with MTX participated in trials conducted almost entirely in North America. Patients not concomitantly treated with MTX participated in trials conducted almost entirely in Europe/Australia/Canada.

The proposed indication for Adalimumab is for "reducing signs and symptoms and inhibiting the progression of structural damage in adult patients with moderately to severely active RA who have had an inadequate response to one or more DMARDs. Adalimumab can be used alone or in combination with MTX or other DMARDs."

Safety data were provided in the BLA for approximately 2000 patients treated with adalimumab through August 31, 2001 for a median of 12 months, and were updated through August 31, 2002 for a median of 24 months.

C. Regulatory History

Shortly after the IND (#------) for the study of D2E7 (adalimumab) became effective April 16, 1998, the sponsor submitted adverse event reports of cases of serious infections and deaths occurring in studies in Europe that had occurred prior to the time of the submission but were not provided to the FDA in the IND submission. The nine serious infectious adverse events (AEs) reported while patients were receiving adalimumab included: septic arthritis, post-operative wound infection, interstitial pneumonitis, miliary tuberculosis with pleural effusion, lymphatic tuberculosis, streptococcal pneumonia with empyema, gluteal abscess, forearm abscess, and multiple antibiotic resistant pneumonia combined with flaring of pre-existing SLE (systemic lupus erythematosus). By delaying the submission of these AEs to the Agency, the FDA was prevented from adequately assessing the risks to the subjects in the proposed clinical investigation. Based on the occurrence of these serious infections in Europe, all D2E7 clinical trials were placed on clinical hold on June 19, 1998, until these safety concerns could be adequately addressed.

Several explanations were provided by the sponsor including: the larger number of serious infections observed occurred among sicker patients, tuberculosis was more common in Europe, some subjects originally suspected of having infections had chronic infections at baseline or had no infections, and some of the subjects would have been excluded from US trials. In Study DE010 (adalimumab with MTX), which was similar to the proposed US Study in inclusion criteria, the incidence of serious infections was much lower. After intensive review of the explanations submitted by the sponsor, the sponsor was requested to initiate new precautions. On this basis, the clinical hold was removed on August 11, 1998 and the proposed study was allowed to proceed. In order to proceed, investigators were to be informed of the possibility of sepsis, to encourage early recognition and appropriate therapy and include information stating a potential increased risk of infections in the Informed Consent.

In December 1999, the Agency noted that eight cases of tuberculosis had been submitted as expedited safety reports. These tuberculosis cases occurred among 477 patients (1.7% incidence) administered adalimumab in Europe. The Agency requested the sponsor to provide additional information on these cases and determine whether actions could be taken to avoid further cases. Typically, the cases occurred among heavily–treated patients 58-70 years of age with long-standing RA, 4-6 months after initiating D2E7 therapy, and it was determined in retrospect that 80% of the patients had a baseline chest x-ray highly suspicious for prior tuberculosis. No cases of tuberculosis had been seen in US trials.

The sponsor agreed to proposed trial stopping rules, the appointment of a Data Safety Monitoring Board to review unblinded safety data, initiation of screening measures for pre-existing tuberculosis, prophylactic tuberculosis treatment when appropriate prior to administration of D2E7, and the early reporting of serious and unexpected SAEs to the Agency.

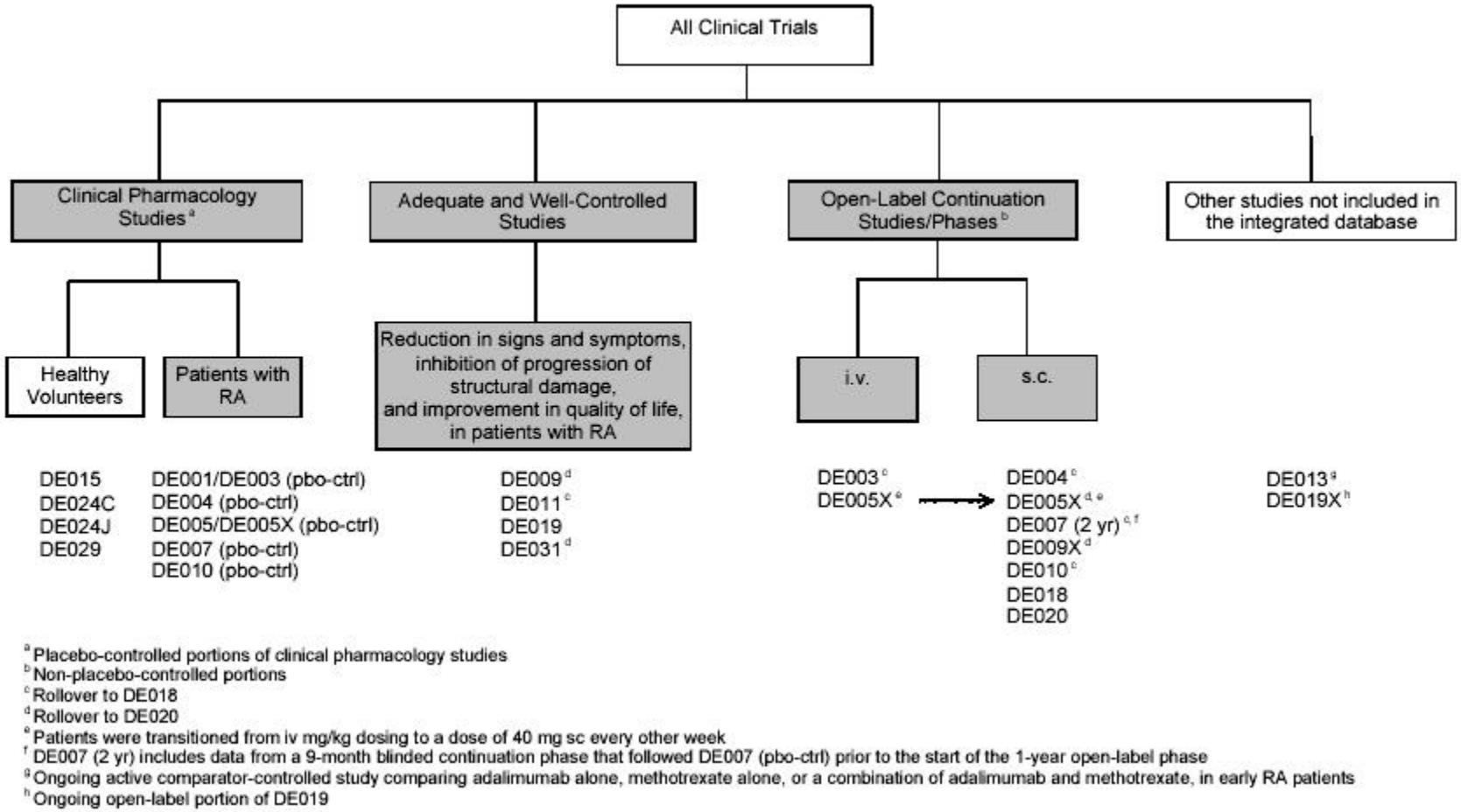

Figure 1: Study groupings for Integrated Summary of Effectiveness Data

Table 1 : Studies Providing Substantial Evidence of Efficacy

Study category	Study	Location	Study characteristics	Dose(s) of adalimumab and route	Duration of study	Number enrolled
Adequate and Well-Controlled Studies	DE009	NA	Multicenter, placebo-controlled, in patients concomitantly treated with MTX	20, 40, or 80 mg every other week, subcutaneous	24 weeks	271
	DE011	EU, AUS, CAN	Multicenter, placebo-controlled, with no concomitant DMARDs	20 or 40 mg, weekly or every other week, subcutaneous	26 weeks	544
	DE019	NA	Multicenter, placebo-controlled, with MTX, investigates joint erosion	20 mg weekly or 40 mg every other week, subcutaneous	52 weeks	619
	DE031	NA	Multicenter, placebo-controlled, with DMARDs, NSAIDs, or steroids	40 mg every other week, subcutaneous	24 weeks	636
Clinical Pharmacology Studies	DE001/DE003 (pbo-ctrl)	EU	Multi-center, placebo-controlled, single dose	0.5, 1.0, 3.0, 5.0, or 10.0 mg/kg, intravenous	≥6 weeks	120
	DE004 (pbo-ctrl)	EU	Multicenter, placebo-controlled	0.5 mg/kg weekly, subcutaneous	12 weeks	24
	DE005/DE005X (pbo-ctrl)	NA	Multicenter, placebo-controlled, single dose, with concomitant MTX	0.25, 0.5, 1.0, 3.0, or 5.0 mg/kg, intravenous	≥6 weeks	60
	DE007 (pbo-ctrl)	EU	Multicenter, placebo-controlled	20, 40, or 80 mg weekly, subcutaneous	12 weeks	284
	DE010 (pbo-ctrl)	EU	Multicenter, placebo-controlled, single dose, with concomitant MTX	1.0 mg/kg, intravenous or subcutaneous	≥6 weeks	54

Study category	Study	Location	Study characteristics	Dose(s) of adalimumab and route	Duration of study	Number enrolled
Open-Label Continuation Studies or Phases	DE003	EU	Continuation of DE001/DE003 (pbo-ctrl)	0.5, 1.0, 3.0, 5.0, or 10.0 mg/kg every other week, intravenous	24 months	117
	DE004	EU	Continuation of DE004 (pbo-ctrl)	0.5 or 1.0 mg/kg weekly, subcutaneous	2.5 years	22
	DE005X	NA	Continuation of DE005 in RA patients concomitantly treated with MTX	All patients transition to 40 mg every other week, subcutaneous	26 months	58
	DE007 (2 yr)[a]	EU	Open-label continuation of DE007 (1 yr), with 3 dose levels in RA patients	20, 40, or 80 mg weekly, subcutaneous	2 years	271
	DE009X	NA	Continuation of DE009, in patients concomitantly treated with MTX	40 mg every other week, subcutaneous	8 months	250
	DE010	EU	Continuation of DE010 (pbo-ctrl), in RA patients with concomitant MTX	1.0 mg/kg every other week, subcutaneous	2.5 years	53
	DE018	EU, AUS, CAN	Continuation for European studies DE003, DE004, DE007, DE010, DE011	40 mg every other or 40 mg weekly, subcutaneous	96 weeks	794
	DE020	NA	Continuation for North American studies DE005X, DE009X, and DE031	40 mg every other week, subcutaneous	Open-ended	810

AUS: Australia; EU: Europe; NA: North America (including U.S. and Canada); CAN: Canada. MTX = methotrexate

[a] Includes a 9-month blinded continuation period that followed DE007 (pbo-ctrl) prior to the start of the open-label phase.

II. Study DE009 - Dose-Ranging Trial

A. Clinical Trial Design – DE009

Study DE009 is a phase II 24 week multicenter double blind randomized placebo-controlled dose-ranging trial to evaluate therapeutic effects, safety, tolerability, and immunogenicity of adalimumab administered subcutaneously every other week with concomitant MTX among patients with a confirmed diagnosis of rheumatoid arthritis. Patients were required to have insufficient efficacy or significant toxicity with MTX at weekly doses 12.5 to 25 mg. The dose of MTX had to be stable for at least 4 weeks before a patient could be screened. Patients receiving 10 to 12.5 mg MTX with documented intolerance to higher doses could also be enrolled. The dose of MTX was to remain constant during the 24-week study period. Patients must have been receiving MTX for at least 6 months before screening.

The study objective is to investigate whether every other week subcutaneous (sc) treatment with 20, 40, or 80 mg adalimumab for up to 24 weeks results in a significantly higher ACR20 response rate compared to treatment with placebo over the same treatment period.

The primary efficacy endpoint of this study was the American College of Rheumatology 20% (ACR20) response as reported at Week 24. A patient was given the classification of "responder" to ACR20 if all of the following criteria were met:

- A $\geq$ 20% improvement in TJC (tender joint count).
- A $\geq$ 20% improvement in SJC (swollen joint count).
- A $\geq$ 20% improvement in three of the five remaining ACR core set measures:
    1. Patient assessment of pain.
    2. Patient global assessment of disease activity.
    3. Physician global assessment of disease activity.
    4. Patient self-assessed disability (disability index of the Health Assessment Questionnaire [HAQ]).
    5. Acute phase reactant (C-reactive protein [CRP]).

Patients who did not meet all of the above criteria, as well as those who withdrew from the study prior to Week 24 (i.e., prior to the end of the placebo-controlled period) were classified as "non-responders." Each patient who withdrew from the study prior to Week 24 due to an AE was counted as a non-responder.

Secondary efficacy endpoints included ACR50 and ACR70, time to response for ACR20, ACR50, ACR70, ACR-N [defined as the least percent improvement (from baseline) in number of 1) tender and 2) swollen joints, and 3) the median percent improvement in a) pain assessment, b) physician and c) patient global assessment, d) physical function, and e) acute phase reactants, and incorporates all disease activity measures of the ACR response], AUC (area under the curve) for numeric ACR response [defined as the product of numeric ACR multiplied by the time a patient is at that level of improvement, which dynamically measures improvement over time (area under the curve of numeric ACR

over time)], tender joint count (TJC) – an assessment of 68 joints or regions done by pressure or joint manipulation on physical examination, swollen joint count (SJC) – An assessment of 66 joints done by physical examination, assessment of pain, Patient Global Assessment of disease activity, Heath Status (Disability Index of the HAQ), Functional Assessment of Chronic Illness Therapy (FACIT), and serologic evaluations, which included cytokine levels (IL-1β, IL-6, and TNF), rheumatoid factor (RF), and markers for cartilage destruction (proMMP-1 and proMMP-3).

B. Study Conduct – DE009

A total of 336 patients were screened, 271 patients were randomized, and 253 completed the study (at least 16 weeks of treatment). Planned enrollment was for 268 patients. Due to the fact that one of the investigators was in the process of being debarred, the eleven (11) patients enrolled at his site were removed from the efficacy analysis. As a result, the efficacy analysis consisted of 260 patients and the demographic and safety analyses include 271 patients. A total of 209 patients received adalimumab and 62 patients received placebo. Figure 2 summarizes the planned conduct of the study.

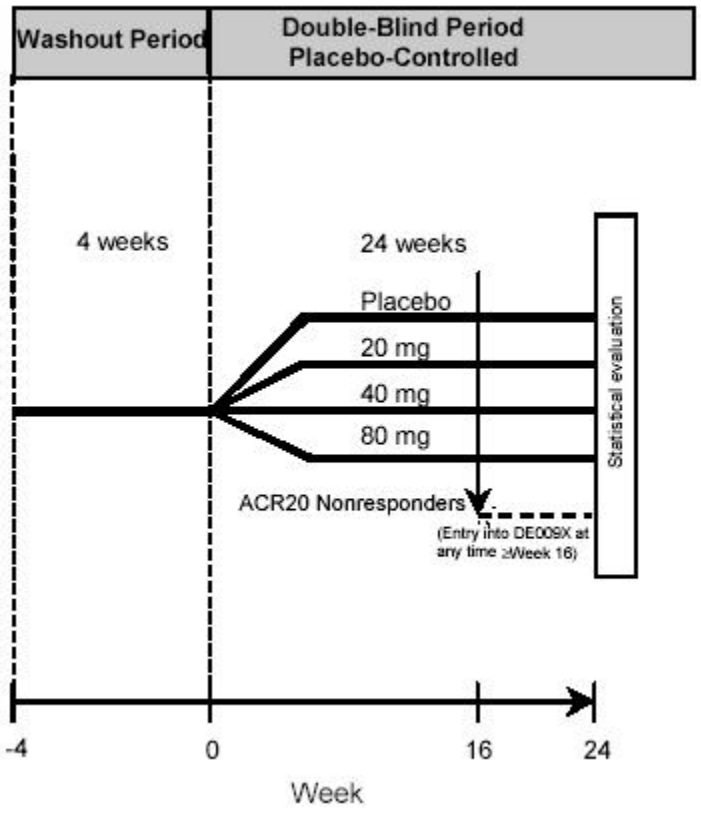

Figure 2 : Design of Study DE009

The Statistical Analysis Plan (SAP) consisted of an efficacy analysis on the intent-to-treat (ITT) population of all patients who were randomized, received at least one injection of double-blind study drug, and for whom any assessment of efficacy under double-blind conditions was available. The primary efficacy analysis consisted of a comparison of the change in ACR20 response rates at Week 24 compared to placebo on the intent-to-treat population. The ACR20 response rates of the three adalimumab groups were compared with the placebo group rates. Dunnett's method, with an overall alpha level of 0.05, was used to adjust for the multiple comparisons of each active treatment group with a single control. Thus, statistical significance required demonstration of a proportionally greater level of efficacy for additional comparisons.

C. Efficacy Analysis

The primary efficacy assessment was a comparison of the ACR20 response rates (using CRP as the acute phase reactant) between the individual adalimumab treatment groups (20, 40, and 80 mg subcutaneous every 2 weeks) and placebo at Week 24 utilizing Dunnett's method to adjust for the multiple comparisons. After 24 weeks of treatment, each adalimumab treatment group (20, 40, and 80 mg) was statistically significantly superior ($p = 0.05$) to placebo for the ACR20 response. The response at Week 24 was comparable between the 40 mg (67%) and 80 mg (66%) doses, was slightly lower for the 20 mg (48%) dose, and was significantly lower for the placebo (13%) (Table 2).

Table 2 : Study DE009: ACR20 response: Number (%) of patients responding over time by randomized treatment group (full analysis set, excluding Site #7)

		Adalimumab		**Placebo**
	20 mg	**40 mg**	**80 mg**	
Time point	(N=67)	(N=63)	(N=70)	(N=60)
Week 24 (observed)	32 (48%)[a]	**42 (67%)[a]**	46 (66%)[a]	**8 (13%)**
LOCF Week 24	34 (51%) [a]	**42 (67%) [a]**	46 (66%) [a]	**8 (13%)**

[a] Statistically significantly different from placebo ($p=0.05$).

As a secondary analysis provided for in the protocol, the last observation was also carried forward (LOCF) to Week 24 for patients who withdrew from the study for reasons other than AEs or those who went into open-label treatment prior to Week 24. Week 24 LOCF data demonstrated similar values between adalimumab and placebo relative to observed values (Table 2). In comparison, fewer placebo-treated patients showed improvement at Week 24.

Adalimumab-treated patients achieved higher ACR50, and ACR70 responses than placebo-treated patients (Table 3).

Table 3 : Study DE009 : ACR50 and ACR70 Responses By Randomized Treatment Group

	Adalimumab			Placebo
Time point	**20 mg** (N=67)	**40 mg** (N=63)	**80 mg** (N=70)	(N=60)
ACR50				
Week 24 (observed)	22 (33%)	**34 (54%)**	29 (41%)	4 (7%)
LOCF Week 24	22 (32%)	**34 (54%)**	29 (41%)	4 (7%)
ACR70				
Week 24 (observed)	7 (10%)	**15 (24%)**	13 (19%)	2 (3%)
LOCF Week 24	7 (10%)	**15 (24%)**	13 (19%)	2 (3%)

* Statistically significantly different from placebo (p=0.05).

Adalimumab-treated patients achieved ACR20 responses faster and more often than placebo-treated patients. ACR20 responses are displayed graphically for the full analysis set of patients in Figure 3. Overall, the adalimumab treatment groups had a higher response at each time point compared to placebo. There is separation between adalimumab- and placebo-treated patients as early as Week 1, and the separation continues through Week 24.

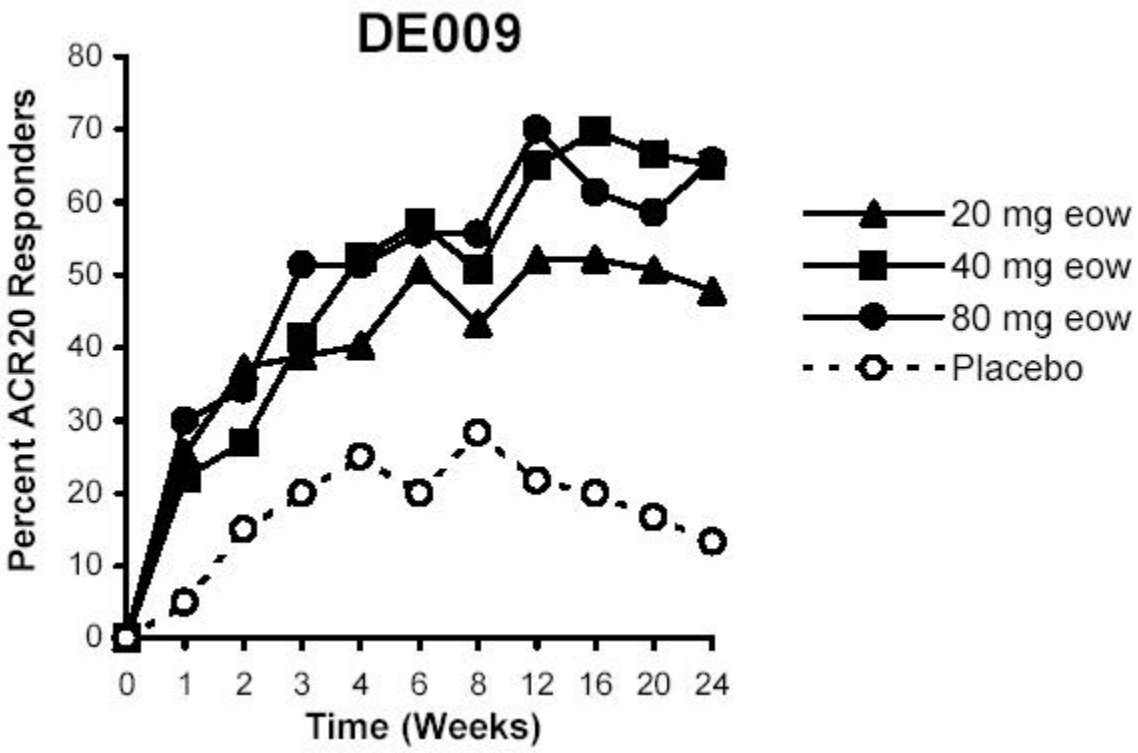

Figure 3 : Study DE009: Responder Rates to ACR20

III. Study DE011

A. Clinical Trial Design

Clinical trial DE011 is a Phase III 26 week adalimumab monotherapy trial to evaluate efficacy, safety, and immunogenicity of two doses (20 and 40 mg) and two dosing intervals (weekly and biweekly) administered subcutaneously in patients with rheumatoid arthritis with single DMARD failure. The doses of 20 and 40 mg adalimumab were selected based on results of a previous study (DE007). DE011 is a multicenter randomized placebo-controlled study comparing adalimumab *vs.* placebo with four periods: 1.) washout period, 2.) placebo-controlled treatment period, 3.) rescue period and 4.) post-study period (Figure 4). After the study entry screen visit, eligible patients entered a 4-week washout period in which all disease-modifying anti-rheumatic drugs (DMARDs) were discontinued. After the washout period, patients were randomized at the baseline visit to one of five treatment arms.

Patients who experienced an increase in disease activity or had less than 10% reduction in SJC and TJC compared to baseline, after at least 8 weeks of treatment, had the option to enter the rescue part of the study. During the rescue part double-blind treatment was stopped, and at the discretion of the treating physician higher doses of steroids, non-steroidal anti-inflammatory drugs (NSAIDs), or DMARDs were prescribed to cover the time until the end of the 26-week placebo-controlled treatment period.

The main criteria for inclusion are male and female patients =18 years of age with a confirmed diagnosis of RA (as defined by the 1987-revised ACR criteria), having failed one DMARD treatment, with at least 10 swollen joints (out of 66 assessed) and 12 tender joints (out of 68 assessed), and an erythrocyte sedimentation rate (ESR) = 28 mm/1st hour or C-reactive protein (CRP) =2 mg/dL.

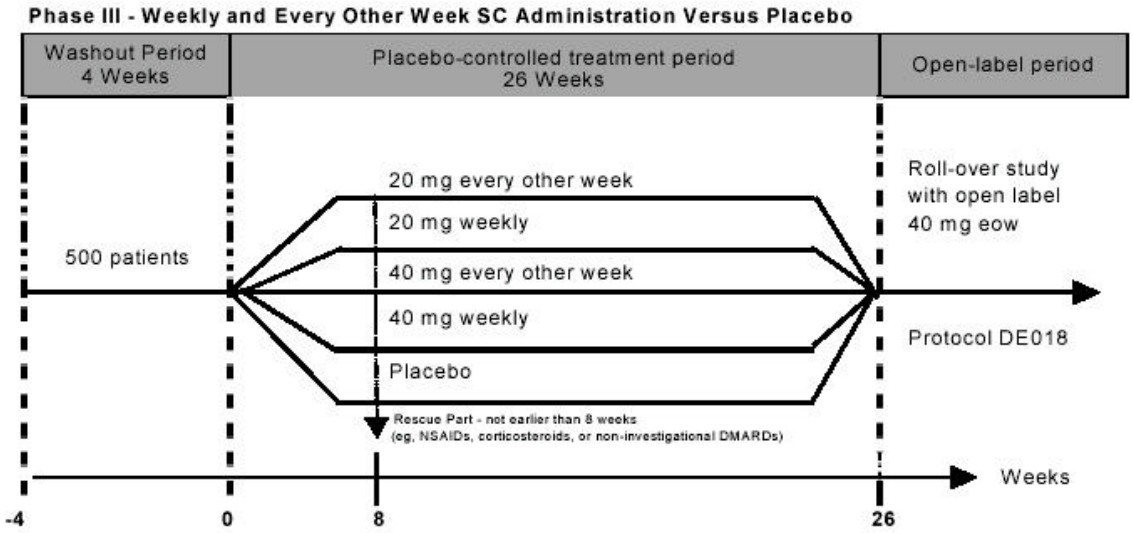

Figure 4: Design of Study DE011

The main exclusion criteria are evidence of cardiac, pulmonary, metabolic, renal, hepatic, gastrointestinal conditions, ongoing, recent, active, or latent infectious diseases, immune deficiency, history of lymphoma, leukemia or solid malignant tumor, history of tuberculosis or listeriosis, drug usage, recent joint surgery or injections, or having previously received any TNF antagonist (e.g., adalimumab, etanercept or infliximab)

Patients were prohibited from receiving any anti-rheumatic/anti-inflammatory drugs (i.e. DMARDs), except stable corticosteroids with a maximum daily dose equivalent to 10 mg of prednisolone, stable doses of NSAIDs prior to entering the rescue part of the study, and infrequent use of acetylsalicylic acid in recommended doses or equivalent treatments for mild pain (e.g., headache) as well as a regular intake of low-dose acetylsalicylic acid for prophylaxis of myocardial infarction.

Adalimumab or placebo was administered as a single sc injection (1.6 mL injectable solution in identical in appearance 2 mL. glass vials) every week or every other week for up to 26 weeks. Based on the randomization scheme, patients were to receive 20 or 40 mg of adalimumab per injection as a total body dose or placebo. Study drug was then injected under the skin of the abdomen or thigh in accordance with standard medical practice for sterile sc injection. The final concentrations of adalimumab were 20 mg/1.6 mL and 40 mg/1.6 mL. Placebo solution was a buffered vehicle of phosphate, citrate, and mannitol with 0.1% Tween 80. Each patient received a weekly injection of study drug or placebo to maintain the blinding.

The primary efficacy assessment was a comparison of the ACR20 response rates (using CRP as the acute phase reactant) between the individual adalimumab treatment groups (20, 40, and 80 mg subcutaneous every 2 weeks) and placebo at Week 24. Statistical methodology consists of Pearson's chi-squared ($?^2$) test and analyses of covariance (ANCOVA) for treatment group differences between adalimumab and placebo during the placebo-controlled treatment period. Baseline homogeneity of demographic and baseline characteristics were checked using one-way analysis of variance (ANOVA), the Kruskal-Wallis test, or a Pearson's $?^2$ test, as appropriate. The primary efficacy analysis was a comparison of the response rates according to ACR20 in the intent-to-treat (ITT) population which was the same as the full analysis set of patients, and patients who did not complete the 26-week placebo-controlled period were counted as non-responders. Each of the four adalimumab dosage groups was tested for difference *vs.* placebo using a two-sided Pearson's $?^2$ test. The overall significance level was $a=0.05$. Multiplicity of testing (four tests) for the primary efficacy analysis was taken into account by applying the Bonferroni-Holm procedure, multiplying by a factor related to the number of comparisons and the degrees of freedom for the error mean square. Thus requiring a four-fold lower p-value in order to acquire statistical significance. All other statistical testing was unadjusted for multiple comparisons.

Analyses of the secondary efficacy endpoints included TJC, SJC, disability index of the HAQ, ACR50 response, ACR70 response, ACR-N response, time until ACR20, ACR50, and ACR70 responses, AUC of ACR-N, ACR20, ACR50, and ACR70 responses, patient and physician global assessments of disease activity, patient assessment of pain, duration of morning stiffness, CRP, ESR, SF-36 score, and modified DAS score. Statistical

analyses of secondary efficacy variables (Pearson's x^2 test for ACR50 and ACR70 response, ANCOVA for other secondary efficacy variables) were exploratory analyses.

B. Study Conduct

A total of 500 patients (100 per arm) were planned for enrollment in this study conducted at 52 sites in Europe, Australia, and Canada. Eight hundred twenty-seven (827) patients were screened, 544 patients were randomized, 481 patients completed the study, and data for 544 patients were analyzed (a larger number of patients than anticipated). Patients were randomized in blocks of five patients per block. Patient disposition is shown in Figure 5 and Table 4.

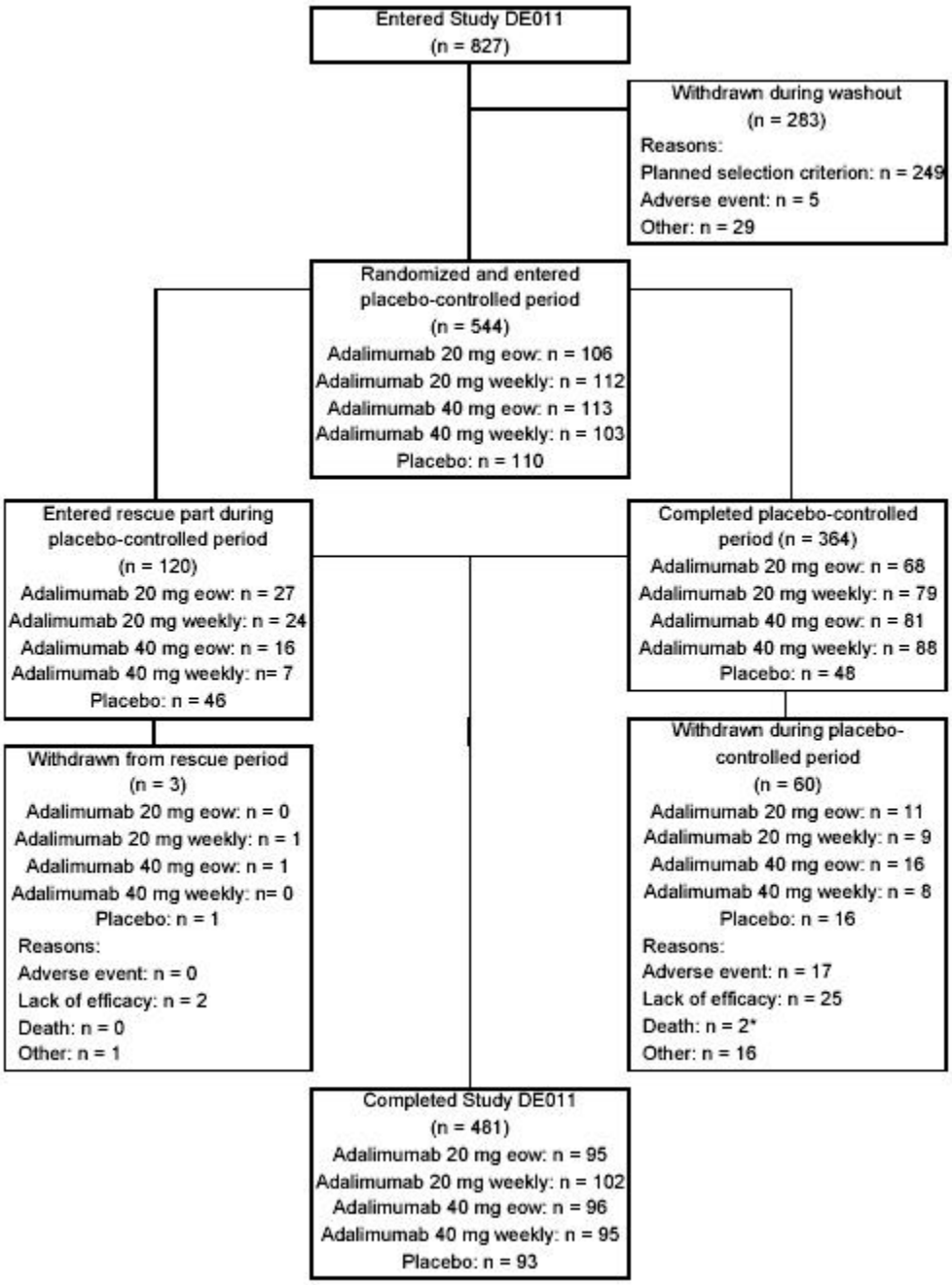

Figure 5 : Patient Disposition in Study DE011

Table 4 : Study DE011 Patient disposition (number [%]) by randomized treatment group (all patients who entered the study)

Treatment	Adalimumab					Placebo
	20 mg		40 mg		All	
	Q2W	Weekly	Q2W	Weekly		
	N=106	N=112	N=113	N=103	N=434	N=110
Completed study	**95 (90%)**	**102 (91%)**	**96 (85%)**	**95 (92%)**	**388 (90%)**	**93 (85%)**
Completed study on randomized therapy	**68 (64)**	**79 (71)**	**81 (72)**	**88 (85)**	**316 (73)**	**48(44)**
Completed study with rescue = 8 weeks	27 (26)	23 (21)	15 (13)	7 (7)	**72 (17)**	**45(41)**
Withdrew early	11 (10)	10 (9)	17 (15)	8 (8)	46 (11)	17(16)
Withdrawals from study due to :						
Adverse event	4 (4)	3 (3)	6 (5)	3 (3)	16 (4)	1 (1)
Lost to follow-up	0 (0)	0 (0)	1 (1)	0 (0)	1 (0)	1 (1)
Protocol violation	2 (2)	2 (2)	2 (2)	1 (1)	7 (2)	1 (1)
Death	0 (0)	0 (0)	1 (1)	0 (0)	1 (0)	1 (1)
Withdrawal of consent	1 (1)	1 (1)	2 (2)	1 (1)	5 (1)	2 (2)
Lack of efficacy/progression of disease	4 (4)	4 (4)	5 (4)	3 (3)	16 (4)	11(10)
Adverse event (at least possibly drug-related)	3 (3)	3 (3)	4 (4)	2 (2)	12 (3)	0

A total of 364 (67%) of 544 randomized patients completed the placebo-controlled portion of the adalimumab monotherapy trial. Similar proportions of subjects completed the study in the drug and placebo arms. However, a higher percentage of adalimumab-treated patients completed the study (64 - 85%) on randomized therapy compared to placebo-treated patients (44%). A total of 120 patients (22%) entered the rescue part during the placebo-controlled period. However, three of the patients requiring rescue withdrew prematurely, and 117 patients requiring rescue completed the study. A higher percentage of placebo-treated patients (41%) than adalimumab-treated patients (17%) required rescue therapy after the 8th week.

A higher percentage of placebo-treated patients (16%) than adalimumab-treated patients (11%) withdrew from the study early. This difference is accounted for by a higher proportion of placebo-treated patients (10%) than adalimumab-treated patients (4%) withdrawing for lack of efficacy. Among the 46 adalimumab-treated patients who withdrew from the study, 16 (4% of those randomized) patients withdrew due to adverse events and 16 (4% of those randomized) withdrew due to lack of efficacy/progression of disease. Among the 17 (16% % of those randomized) placebo-treated patients who withdrew from the study, 11 (10% of those randomized), the majority, withdrew due to lack of efficacy/progression of study disease.

Adverse events, at least possibly drug-related, were observed in 3% (12/434) of adalimumab-treated patients and 0% of placebo-treated patients. Two deaths occurred in the trial, one among each group, the adalimumab-treated group and placebo-treated group. Deaths and adverse events will be reviewed in the Integrated Safety Analysis.

Protocol violations contributing to withdrawals occurred in 2% of adalimumab-treated patients and 1% of placebo-treated patients.

The demographic characteristics (see Table 5) by randomized treatment group for all patients who entered the study demonstrated that the majority were Caucasians and 80% were females with a median age of 54 years, similar to other RA clinical trials. The demographic characteristics in the various groups were comparable. Participants manifested long-standing disease (medians 8-10 years) and active rheumatoid arthritis, as manifested by high mean TJCs (means 34-36) and SJCs (means all approximately 20) (Table 6).

Table 5 : Study DE011 : Demographic characteristics by randomized treatment group (all patients who entered the study)

Demographic Characteristic	Adalimumab					Placebo
	20 mg eow (N=106)	20 mg weekly (N=112)	40 mg eow (N=113)	40 mg weekly (N=103)	All adalimumab (N=434)	(N=110)
Age (years)						
Mean ± SD	53.1 ± 12.2	54.4 ± 11.8	52.7 ± 13.3	51.8 ± 11.8	53.0 ± 12.3	53.5 ± 13.2
Median (range)	55 (24-78)	55 (25-79)	54 (19-80)	52 (28-78)	54 (19-80)	55 (21-78)
Age group N(%)						
<40	16 (15.1)	15 (13.4)	24 (21.2)	18 (17.5)	73 (16.8)	20 (18.2)
40 – 64	72 (67.9)	72 (64.3)	68 (60.2)	70 (68.0)	282 (65.0)	65 (59.1)
65 – 74	14 (13.2)	21 (18.8)	15 (13.3)	11 (10.7)	61 (14.1)	22 (20.0)
≥75	4 (3.8)	4 (3.6)	6 (5.3)	4 (3.9)	18 (4.1)	3 (2.7)
Gender N(%)						
Male	22 (20.8)	31 (27.7)	23 (20.4)	22 (21.4)	98 (22.6)	25 (22.7)
Female	84 (79.2)	81 (72.3)	90 (79.6)	81 (78.6)	336 (77.4)	85 (77.3)
Ethnic origin N(%)						
Black	1 (0.9)	1 (0.9)	1 (0.9)	0 (0.0)	3 (0.7)	0 (0.0)
Caucasian	105 (99.1)	108 (96.4)	109 (96.5)	103 (100)	425 (97.9)	109 (99.1)
Asian	0 (0.0)	2 (1.8)	2 (1.8)	0 (0.0)	4 (0.9)	1 (0.9)
Other	0 (0.0)	1 (0.9)	1 (0.9)	0 (0.0)	2 (0.5)	0 (0.0)
Weight (kg)						
Mean ± SD	68.5 ± 13.2	67.3 ± 13.1	68.8 ± 13.7	69.7 ± 14.5	68.5 ± 13.6	69.8 ± 12.7
Median (range)	67.5 (43-100)	65.5 (41.7-101.5)	69.0 (42-100)	67.0 (44-100)	67.0 (41.7-101.5)	70.0 (42-99)
Height (cm)						
Mean ± SD	164.5 ± 8.0	165.1 ± 8.2	165.5 ± 8.2	164.9 ± 9.6	165.0 ± 8.5	165.1 ± 9.3
Median (range)	164 (148-187)	165 (146-189)	165 (148-197)	165 (147-192)	165 (146-197)	165 (144-189)
BMI (kg/m^2)						
Mean ± SD	25.3 ± 4.7	24.5 ± 4.2	25.1 ± 4.8	25.6 ± 4.5	25.1 ± 4.5	25.6 ± 4.4
Median (range)	23.9 (17.4-39.4)	24.1 (16.9-34.9)	24.5 (15.4-38.8)	25.0 (17.7-38.0)	24.4 (15.4-39.4)	25.0 (17.7-38.3)

BMI = Body Mass Index = Body weight (kg) / [height (m)]^2

eow = every other week

Table 6 : Study DE011 : Duration of RA and ACR components of disease activity at baseline by randomized treatment group (full-analysis set)

Disease Activity Parameter	Adalimumab 20 mg eow (N=106)	Adalimumab 20 mg weekly (N=112)	Adalimumab 40 mg eow (N=113)	Adalimumab 40 mg weekly (N=103)	All adalimumab (N=434)	Placebo (N=110)
Duration of RA [years]						
Mean ± SD	9.3 ± 6.4	11.3 ± 8.6	10.6 ± 6.9	11.9 ± 8.8	10.8 ± 7.8	11.6 ± 9.3
Median (range)	7.7 (0.3-28.9)	8.6 (0.2-35.0)	10.0 (0.3-29.0)	10.4 (0.3-44.8)	9.0 (0.2-44.8)	10.1 (0.6-45.2)
Tender joint count						
Mean ± SD	33.9 ± 14.4	35.3 ± 14.9	33.7 ± 15.9	33.8 ± 14.0	34.2 ± 14.8	35.5 ± 14.2
Median (range)	32.0 (7-67)	33.0 (9-68)	31.0 (2-68)	34.0 (9-68)	32.0 (2-68)	35.0 (5-68)
Swollen joint count						
Mean ± SD	19.6 ± 8.7	19.8 ± 9.7	20.5 ± 10.6	19.3 ± 8.8	19.8 ± 9.5	19.8 ± 9.3
Median (range)	18.0 (7-47)	18.0 (4-53)	18.0 (3-57)	18.0 (3-46)	18.0 (3-57)	18.5 (5-50)
Patient assessment of pain [mm on VAS]						
Mean ± SD	73.8 ± 18.2	71.1 ± 21.0	70.1 ± 19.9	71.2 ± 19.1	71.5 ± 19.6	70.2 ± 18.1
Median (range)	76.0 (14-100)	74.5 (15-100)	73.0 (10-100)	75.0 (16-100)	75.0 (10-100)	73.0 (14-100)
Patient assessment of disease activity [mm on VAS]						
Mean ± SD	75.1 ± 18.2	74.0 ± 20.1	72.5 ± 19.3	74.2 ± 18.7	73.9 ± 19.1	71.8 ± 19.9
Median (range)	77.0 (11-100)	79.0 (16-100)	75.0 (18-100)	77.0 (27-100)	77.0 (11-100)	75.0 (17-100)
Physician assessment of disease activity [mm on VAS]						
Mean ± SD	69.6 ± 17.6	68.1 ± 17.5	67.0 ± 16.7	67.7 ± 17.0	68.1 ± 17.2	68.5 ± 18.2
Median (range)	72.5 (24-100)	70.0 (25-100)	66.0 (31-100)	70.0 (24-97)	70.0 (24-100)	70 (15-99)
Disability index of the HAQ						
Mean ± SD	1.88 ± 0.60	1.88 ± 0.63	1.83 ± 0.59	1.84 ± 0.57	1.86 ± 0.60	1.88 ± 0.64
Median (range)	1.88 (0.38-3.0)	1.88 (0.5-3.0)	1.88 (0.38-3.00)	1.88 (0.50-2.88)	1.88 (0.38-3.00)	2.00 (0.13-3.00)
ESR (mm 1st hour)						
Mean ± SD	52.8 ± 27.9	51.5 ± 24.8	55.8 ± 27.0	51.1 ± 25.0	52.8 ± 26.2	56.1 ± 28.0
Median (range)	45.0 (8-130)	48.0 (14-120)	54.0 (10-125)	49.0 (3-125)	50.0 (3-130)	50.5 (4-132)
CRP (mg/L)						
Mean ± SD	52.4 ± 52.1	47.2 ± 37.6	52.6 ± 37.4	49.3 ± 40.4	50.4 ± 42.1	57.0 ± 49.0
Median (range)	37.6 (3.5-248.0)	37.6 (3.5-178.0)	46.2 (3.5-190.0)	42.0 (3.5-230.0)	40.1 (3.5-248.0)	39.2 (3.5-253.0)
Modified DAS score						
Mean ± SD	7.08 ± 0.92	7.09 ± 0.86	7.07 ± 0.86	7.02 ± 0.81	7.06 ± 0.86	7.09 ± 0.87
Median (range)	7.14 (5.17-8.92)	7.04 (5.05-8.68)	7.14 (5.15-8.81)	7.15 (4.22-8.51)	7.10 (4.22-8.92)	7.15 (4.87-9.08)

C. Efficacy Analysis

1. Efficacy Endpoints

The primary efficacy endpoint was the ACR20 response at Week 26. Patients were classified as "**responders**" if all of the following criteria were met:

- A ≥20% improvement in tender joint count.
- A ≥20% improvement in swollen joint count.
- A ≥20% improvement in at least three of the five remaining ACR core set measures:
    1. Patient assessment of pain.
    2. Patient global assessment of disease activity.
    3. Physician global assessment of disease activity.
    4. Patient self-assessed disability (disability index of the Health Assessment Questionnaire [HAQ]).
    5. Acute phase reactant: ESR or C-Reactive Protein.

Patients were considered to be **non-responders** (efficacy failures) if they:

- failed to meet or improve beyond the American College of Rheumatology 20% (ACR20) improvement criteria at Week 26
- withdrew from the study prior to Weeks 26 (including ACR20 responders),
- switched to rescue medication

Rescue medication was permitted after 8 weeks if patients experienced an increase in disease activity or had less than 10% reduction in SJC and TJC compared to baseline. Leflunomide was the preferred rescue treatment if available in the site's given country. Additional rescue medications permitted through the remainder of the 26-week placebo controlled treatment period included: higher doses of NSAIDs, corticosteroids, or DMARDs.

Secondary efficacy endpoints included changes in SJC, TJC, and disability index of the HAQ from baseline to Week 26; ACR50, ACR70, numeric ACR (ACR-N), disease activity score (DAS), patient and physician global assessments of disease activity, patient assessment of pain, morning stiffness, short form health survey (SF-36), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), rheumatoid factor (RF), and parameters derived from the variables mentioned above.

Serum adalimumab and human anti-human antibodies (HAHAs) concentrations were measured.

2. Efficacy Analysis

The full analysis set comprised all randomized patients who received at least one injection of study drug and for whom any assessment of efficacy under double-blind treatment was available. This was the case for a total of 544 patients enrolled in this study: 434 patients were administered adalimumab and 110 patients were administered placebo.

A dose response for ACR20 response rates was observed across the adalimumab treatment groups at Week 26, with the lowest response rate in the 20 mg q2w group (33%) and the highest observed in the 40 mg weekly group (54%). A summary of the efficacy parameters measured during the study period is included in Table 7. The ACR20 response at the dosage requested for adalimumab approval, 40 mg q2w, demonstrated statistically significant superiority over placebo, 43% for adalimumab compared to 20% for placebo ($p = 0.001$). The 40 mg weekly treatment group showed a higher ACR20 response at Week 26 than the 20 mg q2w treatment group (nominal $p=0.011$) and the 20 mg weekly group (nominal $p=0.038$). All other between-group adalimumab comparisons were not statistically significantly different. It should be noted that these analyses, and all future presentations of between adalimumab group differences, are exploratory since the study was not designed to detect significant differences between adalimumab treatment groups.

The primary efficacy assessment for this study was a comparison of the ACR20 response rates (using CRP as the acute phase reactant) between each of the adalimumab treatment groups and placebo at Week 26. After 26 weeks of treatment, every adalimumab treatment group (weekly and q2week treatment with 20 or 40 mg) was statistically significantly superior ($p \geq 0.05$) to placebo for the ACR20 response (20 mg q2w: $p=0.006$; 20 mg weekly: $p \geq 0.001$; 40 mg q2w: $p \geq 0.001$; 40 mg weekly: $p \geq 0.001$). These p-values are significant even when judged against the Bonferroni-Holm procedure.

Analyses of the secondary efficacy endpoints included TJC, SJC, disability index of the HAQ, ACR50 response, ACR70 response, ACR-N response, time until ACR20, ACR50, and ACR70 responses, AUC of ACR-N, ACR20, ACR50, and ACR70 responses, patient and physician global assessments of disease activity, patient assessment of pain, duration of morning stiffness, CRP, ESR, SF-36 score, and modified DAS score. Statistical analyses of secondary efficacy variables (Pearson's x^2 test for ACR50 and ACR70 response, ANCOVA for other secondary efficacy variables) were exploratory analyses.

Table 7 : Study DE011 : Components of ACR 20 Response Index

(Median Percentage Improvement at Week 26 Compared to Baseline [a])

Efficacy Parameter	Adalimumab				Placebo
	20 mg		40 mg		
	eow	weekly	Q2w	weekly	
N =	106	112	113	103	110
ACR 20 response [o]	(33%)*	(38%)**	(43%)***	(54%)***	(20%)
TJC mean percent change [c]	42%*	47%***	50%**	57%***	13%
SJC mean percent change [c]	33%*	44%***	43%***	53%***	14%
1.Pain VAS [c]	22 [ns]	34***	44***	57***	8
2. Patient global assessment [c]	21 [ns]	36***	40***	57***	9
3. Physician global assessment [c]	25**	44***	52***	62***	12
4. HAQ [c]	10**	15***	13***	27***	0
5. Acute phase reactant [c] CRP	20 [ns]	47*	49***	55***	-2
Duration of morning stiffness	50 [ns]	67**	75***	88***	33

Due to the multiple testing (four tests), the Bonferroni-Holm procedure was applied to keep the overall level of significance $\alpha = 0.05$ for the primary efficacy parameter..

*** Comparison versus placebo (2-sided) p = 0.05.**
**** Comparison versus placebo (2-sided) p = 0.01.**
***** Comparison versus placebo (2-sided) p = 0.001.**
[ns] not significant
[a] Negative values indicate worsening
[o] Observed values; non-responders imputation; comparisons vs placebo by Pearson's chi-square test
[c] LOCF; Median percentage improvement -comparisons vs placebo by ANCOVA with factor treatment group and baseline value as covariate Comparisons versus placebo (2-sided)

After 26 weeks of treatment, each adalimumab dose was associated with a greater median percentage improvement (negative change from baseline) in TJC, SJC, and the disability index (HAQ) than placebo. The TJC, SJC, pain (VAS), patient global assessment, physician global assessment, acute phase reactant, duration of morning stiffness, and the disability index of the HAQ responses at the dosage requested for adalimumab approval, 40 mg q2w, demonstrated statistically significant superiority for adalimumab compared to placebo (p = 0.01).

Since rescue was allowed after Week 8 for patients experiencing lack of efficacy, it is informative to examine response rates at Week 8, when all subjects were still receiving assigned study drug. Table 8 compares the ACR20 response at Week 8 (the time period at which rescue medication was initially permitted) and Week 26 (the time period for appraisal of the primary efficacy endpoint). At Week 8, before rescue medication was allowed, the majority of the ACR20 responses to adalimumab at the proposed dosage of 40 mg biweekly had already been demonstrated, and only a few additional responses occur over the next 18 weeks.

Table 8 : Study DE011 : Comparison of ACR20 Response At Week 8 and Week 26

	Adalimumab				
ACR 20 Responders at	**20 mg q2w**	**20 mg weekly**	**40 mg q2w**	**40 mg weekly**	**Placebo**
Week 8	43 (41%)	46 (41%)	46 (41%)	45 (44%)	16 (15%)
Week 26	38/106 (36%)	44/112 (39%)	52/113 (**46%**)	55/103 (**53%**)	21/110 (**19%**)

Figure 6 displays graphically the observed ACR20 responses over time for the full analysis set of patients. This figure demonstrates that the majority of responders had achieved an ACR20 response by the Week 2 study visit. In addition, the separation between adalimumab-treated patients and placebo-treated patients continues through Week 26.